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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/769,218	01/30/2004	Yigong Shi	112911.151	9564

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EXAMINER	
KIM, ALEXANDER D	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 10/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/769,218	SHI, YIGONG	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 26-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/09/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *SEQ Alignment*.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on February 7, 2005), Applicants filed a response received on 08/24/2006. Claims 1-52 are pending in this instant Office action.

Election

2. Applicant's election with traverse of Group II, (Claims 20-25) in the reply filed on 08/24/2006 is acknowledged. The traversal is on the ground(s) that the Office has not shown that a burden exists in searching the entire application. This is not found persuasive because each Group represents a distinct independent invention and the search burden exist by the virtue of different class and/or subclass between distinct inventions. Also, the search for each Group requires different key words because divergent subject matters on application. Searching altogether would create serious search burden on the examination. The requirement is still deemed proper and is therefore made FINAL.

Claims 1-52 are pending in the instant application. Claims 1-19 and 26-52 are withdrawn from consideration as non-elected inventions. Claims 20-25 will be examined herein.

Priority

3. Applicant's claim for the benefit of provisional application 60/443,590 (filed on 01/31/2003) under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

No foreign priority under 35 U.S.C. 119(a)-(d) has been filed.

The provisional application 60/443590 does not have any support for the instant application, thus instant filing date of 01/30/2004 is the priority date for the instant application.

Information Disclosure Statement

4. The information disclosure statement (IDS) filed on 08/09/2004 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Objections to the Specification

5. The specification is objected to because of the following informalities:

a. The specification is objected to because the title is not descriptive of the claims. A new title is required that is clearly indicative of the invention to which the claims are drawn (see M.P.E.P. § 606.01). The examiner suggests the following new title, for example:

---A method of inhibiting the activity of caspase-9 with a polypeptide from BIR3---

b. The Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the source species (human) for completeness.

c. The instant application disclose provisional application 60/443,950. There is an error in the application number. It should be 60/443,590. Appropriate correction is required.

d. The specification recite "the catalytic subunit of caspase-9 (residues 139-416, in vector pET-21b)" (see p. 33 line 14). However, the instant catalytic subunit of caspase-9 of sequence SEQ ID NO: 1 contains residues from 140 to 416 (see SEQ Alignment). Appropriate clarification is required.

e. The specification recite "BIR3 domain of XIAP (residues 252-350, in vector pBB75)" (see p. 33 line 15). However, the instant catalytic subunit of caspase-9 of sequence SEQ ID NO: 2 contains residues from 253 to 350 (see SEQ Alignment). Appropriate clarification is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 20-25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 20 and 24 recite the limitations of amino acid residues P325, G326, H343 and L344. It is unclear if the polypeptide having a surface groove requires only said four residues as a part of linear polypeptide (i.e. polypeptide comprising $P_{325}G_{326}$ --- $H_{343}L_{344}$ which requires a SEQ ID NO) or the polypeptide having surface groove defined by the said four residues in a particular orientation respect to each other which requires a three-dimensional structure coordinate data. Appropriate clarification is required.

7. Claim 20-25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 20 and 24-25 have parentheses and it makes claims 20 and 24-25 unclear if these residues must be included or not particularly since "mammalian" is unlikely to refer to a single SEQ ID NO. Appropriate clarification is required.

8. Claims 24 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 recites the limitation "inhibiting effector

caspase activity". It is unclear if the claim is limited to any particular cascade, pathway and/or proteins by the term. Appropriate clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 20-25 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a method of inhibiting the activity of mammalian caspase-9 by forming 1:1 complex with a BIR3 domain polypeptide having surface groove including P325, G326, H343 and L344 (claim 20, claims 21-23 dependent therefrom) and a method of inhibiting effector caspase activity comprising, combining a mixture of effector caspase with mammalian caspase-9 and a composition comprising a polypeptide forming 1:1 complex with a caspase-9 wherein the polypeptide is BIR3 domain having surface groove including P325, G326, H343 and L344 (claim 24, claim 25 dependent therefrom).

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials."

University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical Inc. v. Gen-Probe Inc.* (CAFC (2002) 63 USPQ2d 1609).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from *Enzo Biochemical* (see above).

The instant specification teach a method for inhibiting a protease activity of human caspase-9 by forming 1:1 complex with the polypeptide of SEQ ID NO: 2 which is a human BIR3 domain comprising P325, G326, H343 and L344 or method of inhibiting a effector caspase (procaspase-3) activity in the mixture containing inactivated

mammalian caspase-9 complex with the polypeptide of SEQ ID NO: 2 which is a BIR3 domain comprising P325, G326, H343 and L344. However, the breadth of claim includes a method of inhibiting a caspase-9 by forming 1:1 complex with any polypeptide having two di-peptide of ProGly and HisLeu which is part of BIR3 surface groove or any polypeptide having a surface groove defined by said four amino acids as described in the co-crystal structure of caspase-9:BIR3 domain; a method of inhibiting caspase effector by combining a mixture containing 1:1 complex of caspase-9 and any polypeptide described above. The prior art and instant specification teach a method of inhibiting human caspase-9 catalytic activity by forming complex with a polypeptide containing BIR domain thus inhibiting human procaspase-3 activity by blocking process of procaspase-3 (Deveraux et al. 1999, The EMBO Journal, Vol. 18 p. 5242-5251). The examples of method described by prior art and instant specification do not describe a method of using any other polypeptide encompassed by the scope of the claims. A method of instant specification and prior arts do not describe a method of inhibiting mammalian caspase-9 activity or effector caspase activity by a genus polypeptide with unlimited structural limitation as long as it contains said four amino acid residues sufficiently to represent the correlation between the structure and function of claimed genus that is a method of inhibition by the genus polypeptide forming 1:1 complex with mammalian caspas-9 and thus inhibiting procaspase-3 activation. Thus the instant specification and the prior art cannot describe the structure of a very broad claimed genus (i.e. a peptide with said four amino acids) and one skilled in the art would not be in possession of the claimed genus polypeptide(s) for the instant methods.

10. Claims 20-25 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method for inhibiting protease activity of mammalian caspase-9 thus inhibiting the procaspase-3 activation by forming 1:1 complex between the caspase-9 and the polypeptide comprising a human BIR3 domain which contains P325, G326, H343 and L344, does not reasonably provide enablement for a method of inhibiting mammalian caspase-9 by forming 1:1 complex with any polypeptide comprising said four amino acids. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use of the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the

presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The nature of the invention is drawn to a method for inhibiting a protease activity of human caspase-9 by forming 1:1 complex with the human BIR3 domain which contains said four amino acid residues thus inhibiting a procaspase-3 activation by the inactivated capspase-9 and BIR3 complex. However, The breadth of claims includes a method of inhibiting mammalian caspase-9 and in turn inhibiting the caspase effector, procaspase-3 for example, activity by forming 1:1 complex with any polypeptide as long as it contains two dipeptide (i.e. ProGly and HisLeu) or said four amino acids. Applicants and the prior art teach one method of inhibiting protease activity of human caspase-9 thus inhibiting procaspase-3 activation with a peptide containing a human BIR3 domain with procaspase-3 as substrate as described in Example 3, p. 35 or Figure 5 of Deveraux et al. The instant specification disclose no direction or guidance on how to inhibit mammalian caspase-9 thus in turn inhibiting procaspase-3 activity by forming 1:1 complex between mammalian caspase-9 and any other polypeptide comprising two dipeptide (i.e. ProGly and HisLeu) or said four amino acids. Thus the specification and prior art fail to describe how to make and use the claimed genus polypeptide sufficiently in claimed methods. Therefore, it is unpredictable for a method of inhibiting mammalian caspase-9 thus in turn inhibiting pro-caspase-3 activation using a polypeptide

encompassed by the instant claims. For all of the above reason, it would require undue experimentation necessary for a method of using the claimed genus of polypeptides.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 20-25 are rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter. Claim 20-25, as written, does not sufficiently distinguish over a steps occur in human cells as they naturally exist because the claims do not particularly point out any non-naturally occurring differences between the claimed product of polypeptide comprising four amino acids (P325, G326, H343 and L344) and the naturally occurring polypeptide of BIR3 domain which also contain said four amino acids. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206, USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g. by insertion of "isolated" or "purified" for proteins used in method as taught by the specification. See M.P.E.P. § 2105.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 20-25 are rejected under 35 U.S.C. 102(b) as being anticipated by as evidenced by Deveraux et al. (1999, The EMBO Journal, Vol. 18, p. 5242-5251) and Shiozaki et al. (2003, Molecular Cell, vol. 11, p. 519-527). Claims 20-23 are drawn to a method of inhibiting the activity of caspase-9 by comprising mammalian caspase-9 and a BIR3 which forms 1 to 1 complex wherein the BIR3 contains amino acid residues of P325, G326, H343 and L344.

KK 10/12/06

Deveraux et al. (1999) teach a method comprising testing the "ability to inhibit purified recombinant active caspases" and disclose a "BIR3-Ring" "inhibit active recombinant caspase-9" (see bottom of left column, p. 5247). The caspase-9 of Deveraux et al. is a human caspase-9. The BIR3-Ring of Deveraux et al. contains the sequence 243-497 compared to the full length of XIAP (as shown in Figure 2), thus contains amino acid residues of P325, G326, H343 and L344 (see SEQ Alignment in the attachment). Deveraux et al. also teach XIAP protein "at equimolar concentration completely inhibits" caspases and the BIR3 domain of Deveraux et al. (1999) would form a inherent 1:1 complex with caspase-9 as shown in "inhibitory complex" from the co-crystal structure by Shiozaki et al. (2003). Deveraux et al. also teach a method of measuring a "caspase activity generated in intact cells" (see bottom of left column, p. 5250) using a "human embryonic kidney 293" "were assayed for apoptosis" thus meets the limitations of claim 21-22. Deveraux et al. teach a method of adding the caspase-9 into the caspase buffer having "10% sucrose" (see bottom of left column, p. 5250), thus

meets the limitation of claim 23 having a method of using composition including excipient as disclosed by examples in the instant specification page 24, lines 1-7. Thus, the method of Deveraux et al. meets the limitations of claims 20-23.

Deveraux et al. also teach a method involved in combining a "GST-BIR3-Ring with endogenous caspases 3 and 9 in cell lysates" (see description of Figure 5, p. 5246) and shows that pro-caspase-3 activity is inhibited by blocking the processing of pro-caspase-3, which is shown by the gel picture of Figure 6-C. Deveraux et al. disclose that XIAP protein (a full length containing BIR3 domain) "suppress caspase-9, thus blocking the effects of Cyto-c/dATP upstream of pro-caspase-3" (see middle of left column, p. 5247). The method of Deveraux et al. teach a method of inhibiting effector caspase activity wherein the effector caspase activity is procaspase-3, thus meet the limitations of claims 24-25.

Additional References

13. The following are cited to complete the record but is not prior art:

a) Shiozaki *et al.* (2003) Mechanism of XIAP-Mediated Inhibition of Caspase-9, Cell, vol. 11, p. 519-527.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim
October 3, 2006

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